

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re patent application of KEREM

Serial No. 09/871,809

Filed: June 4, 2001

For: CONTROL OF GENE EXPRESSION

Group Art Unit: 1653

Examiner: Kam, Chih-Min

DECLARATION
under Rule 132Commissioner of Patents and Trademarks
Washington, D.C. 20231

I, Batsheva Kerem, an Israeli citizen residing at 6/4 Hefroni Street, Mevasseret Zion, Israel, hereby declare:

1. I am currently a Professor of Genetics in the Department of Genetics of the Hebrew University of Jerusalem, Israel.
2. My *Curriculum Vitae* and list of publications are attached herewith as Annex "A". My fields of expertise include general genetics, human genetics, and molecular biology.
3. I am the inventor of U.S. Patent Application No. 09/871,809 (hereinafter "*the application*") and I am familiar with its contents. The application describes a method of treating individuals suffering from a disease resulting from abnormal expression of genes caused by aberrant splicing in cells. This method comprises administering to cells of such individuals an effective amount of an alternative splicing factor (ASF), whereby said abnormal expression shifts towards normal expression of the gene.
4. The specification describes examples, which, together with known methods, enable a person skilled in the art to use ASFs for the treatment of diseases by restoring gene function.
5. The specification also describes correcting the splicing pattern of CFTR *ex vivo* (example 5), in a cell-line derived from a polyp of a CF patient.
6. Furthermore, we have now also used these same methods in order to prove that overexpressing or activating ASFs not only corrects the splicing pattern, but also restores the function of the aberrantly spliced CFTR gene:

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- a) We transfected cells of the 091398K and the 081301K epithelial cell lines (see pg. 15 of the application) with a minigene of a mutated CFTR (3849+10kb C->T mutation), as described in the specification (example 1), and measured CFTR protein channel activity, by looking at Cl⁻ efflux using the fluorescent dye MQAE. We showed that CFTR channel activity is restored towards normal values only after transfection of the cells with the ASF Hira2-B1 (Figs 1 and 2 of Annex "B").
- b) We further showed that this function restoration can also result from modulating splicing by sodium butyrate (an ASF agonist), rather than by overexpressing the ASF gene itself (Fig 3 and 4 of Annex "B").
- c) This approach was also described in the specification, for example in page 5, line 3-6: "i.e. any factor which is known to modulate alternative splicing, for example, those mentioned in the publications referred to in the list of references, such as members of the SR protein family including the SF2/ASF and its antagonists...", and in page 5, lines 8-11: "The ASF may also be an agonist of the above naturally occurring factors, prepared by peptidomimetics, or by screening various libraries of compounds for the isolation, or the construction of an agent which is able to mimic the activity of naturally occurring ASFs." (boldface and underline not in original).

In other words, the specification adequately describes a method that, if followed, can restore the function of an aberrantly spliced gene inside the cell.

7. Furthermore, the methods of cloning genes and expressing them in cells are also considered routine methods in the prior art, and therefore, using different ASFs than described in the specification is also a matter of routine work. Therefore, I believe we have supplied enough information for a person skilled in the art to use any of treatment for any disease that is caused by aberrant splicing, and for any ASF.

8. Although the examples in the application relate to the treatment of cystic fibrosis, the skilled artisan would recognize that this is just an example of the more general concept defined in the claims, and would be able to extrapolate from the specific examples to the general concept described in the Summary of the Invention section of the application and defined in the claims.

9. To summarize, I believe that the application comprises an adequate description

that will enable a person skilled in the art to recognize that the applicants were in possession of the claimed invention.

10. The undersigned declares further that all statements made herein of her own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date:

02/02/2003
Prof. Batsheva Kerem

CURRICULUM VITAE

Name: Kerem Batsheva

Present address: Department of Genetics
The Life Sciences Institute
Givat Ram campus
Jerusalem 91904, Israel

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Personal Data: Date of Birth: 16 March, 1955, Tel Aviv
Marital Status: Married + 3 children

EDUCATION

1976-1979 B.Sc. (Biology) with distinction
The Hebrew University of Jerusalem

1981-1986 Ph.D. Direct doctoral program in the
Department of Genetics
The Hebrew University, Jerusalem, Israel
Supervisor: The late Prof. Menashe Marcus
Co-supervisor: Prof. S. H. and Cedar

EMPLOYMENT AND RELATED TRAINING

1986-1987 Post doctoral Fellow, Department of Genetics
The Hadassah Medical School, Jerusalem, Israel
Supervisor: Professor Tamar Schaap

1987-1990 Postdoctoral Fellow, Department of Human Genetics
the Hospital for Sick Children, Toronto, Canada
Supervisor: Prof. Lap-Chee Tsui

- 1990- Senior Lecturer, Department of Genetics
Life Sciences Institute, The Hebrew University, Jerusalem, Israel.
- 1998- Associate Professor, Department of Genetics,
Life Sciences Institute, The Hebrew University, Jerusalem, Israel.

AWARDS AND FELLOWSHIPS

- 1984 Prize for excellence in teaching.
- 1986-1987 Lady Davis Postdoctoral Fellowship.
- 1988-1990 Restacum Postdoctoral Fellowship, Canada.
- 1990 Alon Fellowship.
- 1992, 1993 Best teacher in Genetics.
- 1993 The Julodan Prize for Contribution to Medicine.
- 1993 Teva Prize for Excellence in Human Genome
- 1996 Joels Senior Lectureship for Excellence
- 1996 Best teacher in Genetics.

INVITED SPEAKER IN INTERNATIONAL MEETINGS

1. 16th International Congress of Genetics, Toronto, Canada, (1988) Mapping of Dnase I sensitive regions on mitotic chromosomes.
2. 33rd Annual American Cystic Fibrosis Conference, Dallas, Texas, (1989)
Cloning of the cystic fibrosis gene.
3. The 40th North American Society of Human Genetics, Baltimore, Maryland, (1989)
Cloning of the cystic fibrosis gene.
4. The 5th Annual North American Cystic Fibrosis Conference, Orlando, Florida, (1991) A termination mutation, W1282X, the most common mutation in the Jewish Ashkenazi CF patient population in Israel, is associated with a severe disease presentation.

5. The 15th International Congress of Biochemistry, Jerusalem, Israel, (1991)
Association of a nonsense mutation (W1282X), the most common mutation in the Ashkenazi Jewish cystic fibrosis patients in Israel, with severe disease presentation.
6. The Franco-Israeli Symposium on Human Genetics, Jerusalem, Israel, (1992)
Genotype-phenotype association in CF.
7. International Seminar on Human Genome Diversity and Congenital Disorders, Kfar-Saba, Israel, (1993) Cystic fibrosis extended haplotype analysis and implication to the selective advantage hypothesis.
8. The 7th International Conferences on Early Prenatal Diagnosis of Genetic Diseases, Jerusalem, Israel, (1994) Screening for cystic fibrosis mutations in the different Jewish ethnic groups.
9. The Franco-Israeli Symposium on Human Genetics, Paris, France, (1994) Molecular explanations for genotype-phenotype association in CF.
10. The 27th Annual Meeting of the European Society of human Genetics, Berlin, Germany, (1995) The molecular basis of non-typical CF presentations.
11. International Symposium of Genetic Diseases: Genes and Population, Elswira, Morocco, (1995) Variable levels of aberrantly spliced mRNA - a cause for disease variability in cystic fibrosis.
12. The 12th International Cystic Fibrosis Congress, Jerusalem, Israel, (1996) Molecular mechanisms underlying disease variability in CF.
13. 10th German Israeli Foundation (GIF) meeting on Cell Biology of Proteins, Dead Sea, Israel, (1996) Molecular explanation for genotype-phenotype correlation in CF
14. The 9th International Congress of Human Genetics (ICHG) Rio de Janeiro, Brazil, (1996) Molecular basis for genotype-phenotype correlation in CF patients carrying splicing mutations.
15. HUGO's 2nd International Genome Summit, Canberra, Australia, (1996) The Human Genome Project in Israel.
16. An International Workshop on the Eugenics Thoughts and Practice: A Reappraisal Towards the End of the Twentieth Century, Jerusalem, Israel, (1997) Cystic fibrosis in Israel.

17. International Congress, Pediatrics in the Community 2000+, Jerusalem, Israel, (1997)
Genetics of Cystic Fibrosis - overview.
18. The Franco-Israeli Symposium on Human Genetic Diseases, Rehovot, Israel, (1998)
Molecular characterization of a common fragile site (FRA7H) on human chromosome 7
by the cloning of an SV40 integration site.
19. The 5th International Union Of Biochemistry and Molecular Biology (IUBMB)
Jerusalem, Israel, (1998) The molecular basis for genome instability- fragile sites as a
model.
20. The 49th American Society of Human Genetics, Denver Colorado, (1998) Partial
penetrance in CFTR mutations.
21. The 1st International Symposium on Fragile sites and Cancer, NIH sponsored, Mayo
Clinic, Rochester, Minnesota (1998) The molecular basis of common fragile sites in the
human genome.
22. The 2nd International Symposium on Fragile sites and Cancer, Mayo Clinic,
Rochester, Minnesota (2000) Identification and replication analysis of common fragile
sites on human chromosome 7. Hints to the mechanism of fragility?
23. The Keystone Symposium on Human Genetics and Genomics, Denver Colorado
(2001) Splicing effect on penetrance.
24. The 24TH European Cystic Fibrosis Society (ECFS), Vienna, Austria, (2001)
Alternative splicing effect on CF penetrance.
25. The Annual Latino-American Cystic Fibrosis Meeting, Florianopolis, Brazil (2001)
splicing regulation as a genetic modifier of cystic fibrosis
26. The 8th European Workshop on Cytogenetics and Molecular Genetics of Human Solid
Tumors, Barcelona, Spain (2002) The role of fragile sites in oncogene amplification.
27. The Annual Meeting of the Italian Human Genetics Society, Verona, Italy (2002) The
complexity of monogenic diseases and modifier genes.
28. EMBO Members Meeting on Frontiers on Molecular Biology, Oslo, Norway, (2002)
Splicing factors can modulate the CFTR function in cells carrying CFTR splicing
mutations.

29. The Annual HUGO meeting, HGM2002, Cancun, Mexico (2003) Plenary lecture:
"Fragile sites and chromosomal instability in the human genome".

CHAIRPERSON IN INTERNATIONAL MEETINGS

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| 1995 | The 9th North American Cystic Fibrosis Conference, Dallas, Texas, Chairperson of the session "Relationship of CFTR Function to Disease Severity". |
| 1996 | The 10th North American Cystic Fibrosis Conference, Orlando, Florida. Chairperson of the session: "Expression and phenotype". |
| 1999 | Human Genome Meeting (HGM) 2000, Vancouver Canada. Chairperson of the workshop: "Disease mechanisms". |
| 2000 | Human Genome Meeting (HGM) 2001, Edinburgh, Scotland. Chairperson of the workshop: "Disease mechanisms". |
| 2001 | Keystone Symposium on Human Genetics and Genomics, Denver Colorado. Chairperson of the session: "Constructing animal models for human disease". |
| 2002 | The unborn child: scientific discoveries, medical and ethical dilemmas, Tel Aviv, Israel. Chairperson of the session: "Genetics-from in-vitro to in vivo" |

INVITED LECTURER IN INTERNATIONAL COURSES

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| 1993 | " <i>Human Genome Diversity</i> ": An international genetic course, in the International Center for Genetic Engineering and Biotechnology, Trieste, Italy. |
| 1998 | " <i>Genomics</i> ": An international course in The 7th Jerusalem Spring School in Life Sciences. |

1999

"Human Genetics": A course for medical and biology students, University of Verona, Italy.

MEMBERSHIP IN INTERNATIONAL BOARDS

- 1992- Member in the editorial board of the *European Journal of Human Genetics*.
- 2000- Elected Member of the Human Genome Organization (HUGO) council
- 2001- Member, European Molecular Biology organization (EMBO).

MEMBERSHIP IN SCIENTIFIC SOCIETIES

1. American Association for the Advancement of Science.
2. American Society for Human Genetics.
3. European Society for Human Genetics.
4. Human Genome Organization (HUGO).
5. Israel Society of Human Genetics.
6. Israel Society of Genetics.
7. Federation of the Israeli Societies of Experimental Biology.

CURRENT ACADEMIC ACTIVITIES IN ISRAEL

National

1. Research advisor for the Minister of Health.
2. Member in the advisory committee to the Israel Science Foundation on: "The Human Genome Project in Israel".
3. The National Helsinki committee, Ministry of Health.

Hebrew University

1. Head, DNA Analysis Center, The Life Sciences Institute,
2. Development Committee, The Life Sciences Institute.
3. Ethical committee for non-medical research (interfaculty).
4. Appointment committee, Medical School, Ein Kerem.
5. Disciplinary committee in molecular biology, for the life sciences and the medical faculties.
6. Director, "Genomics and Bioinformatics" educational program, for M. Sc. and Ph.D. students.
7. Member in the Authority for Research Students.

LIST OF PUBLICATIONS

1. **Kerem B**, Goitein R, Richler C, Marcus M and Cedar H. (1983) In situ Nick Translation Distinguishes between Active and Inactive X Chromosomes. *Nature* 304:88-90.
2. **Kerem B**, Goitein R, Diamond G, Cedar H and Marcus M. (1984) Mapping of DNase I Sensitive Region on Mitotic Chromosomes. *Cell* 38:493-499.
3. Sperling K, **Kerem B**, Goitein R, Kottush-Geiseler V, Marcus M and Cedar H. (1985) DNase I Sensitivity in Facultative and Constitutive heterochromatin. *Chromosoma* 93:38-42.
4. Richler C, Uliel E, **Kerem B** and Wahrman J. (1987) Regions of Active Chromatin Conformation in "Inactive" Male Meiotic Sex Chromosomes of the Mouse. *Chromosoma* 95:167-170.
5. **Kerem B**, Kottusch-Geiseler V, Kalscheuer V, Goitein R, Sperling K and Marcus M. (1988) DNase I Sensitivity of Microtus Agrestis Active, Inactive and Reactivated X Chromosomes in Mouse-Microtus Cell Hybrids. *Chromosoma* (Berl) 96:227-230.
6. **Kerem B**, Goitein R and Schaap T. (1988) Cytological Evidence of Defective Template in the Fragile X Chromosome. *Chromosoma* (Berl) 97:6-10.
7. Rommens JM, Zengerling S, Burns J, Melmer G, **Kerem B**, Plavsic N, Zsiga M, Kennedy D, Markiewicz D, Rozmahel R, Riordan JR, Buchwald M and Tsui L-C. (1988) Identification and Regional Localization of DNA Markers on Chromosome 7 for the Cloning of the Cystic Fibrosis Gene. *Am J Hum Genet* 43:645-663.
8. **Kerem B**, Corey M, Rommens JM, Riordan JR, Tsui L-C and Levison H. (1989) Clinical and Genetic Comparisons of Patients with Cystic Fibrosis, With or Without Meconium Ileus. *J Paediatrics* 114:767-772.
9. **Kerem B**, Buchanan JA, Durie P, Corey M, Levison H, Buchwald M and Tsui L-C. (1989) DNA Marker Haplotype Association with Pancreatic Sufficiency in Cystic Fibrosis. *Am J Hum Genet* 44:827-834.
10. **Kerem B**, Rommens J, Buchanan JA, Markiewicz D, Cox TK, Chakravarti A, Buchwald M and Tsui L-C. (1989) Identification of the Cystic Fibrosis Gene: Genetic Analysis. *Science* 245:1073-1080.

11. Rommens J, Iannuzzi MC, **Kerem B**, Drumm ML, Melmer G, Dean M, Rozmahel R, Cole JL, Kennedy D, Hidaka N, Zsiga M, Buchwald M, Riordan JR, Tsui L-C and Collins FS. (1989) Identification of the Cystic Fibrosis Gene: Chromosome Walking and Jumping. *Science* 245:1059-1065.
12. Riordan JR, Rommens J, **Kerem B**, Alon N, Rozmahel R, Grzelczak Z, Zielenski J, Lok S, Plavsic N, Chou J-L, Drumm ML, Iannuzzi MC, Collins FS and Tsui L-C. (1989) Identification of the Cystic Fibrosis Gene: Cloning and Characterization of Complementary DNA. *Science* 245:1066-1073.
13. Rommens JM, Zengerling-Lentes S, **Kerem B**, Melmer G, Buchwald M and Tsui L-C. (1989) Physical localization of two DNA markers closely linked to the Cystic Fibrosis locus by pulsed field gel electrophoresis. *Am J Hum Genet* 45:932-941.
14. Rosenbloom CL, **Kerem B**, Rommens JM, Tsui L-C, Wainwright B, Williamson R, O'Brien WE and Beaudet AL. (1989) DNA amplification for detection of the XV-2c polymorphism linked to cystic fibrosis. *Nucleic Acids Res* 17:17.
15. Lemma WK, Feldman GL, **Kerem B**, Fernback SD, Zevkovich EP, O'Brien WE, Collins FS, Tsui L-C and Beaudet AL. (1990) Direct mutation analysis for heterozygote detection and prenatal diagnosis of cystic fibrosis. *N Engl J Med* 322:291-296.
16. Rommens JM, **Kerem B**, Greer W, Chang P, Tsui L-C and Ray P. (1990) Rapid nonradioactive detection of the major CF mutation. *Am J Hum Genet* 46:395-396.
17. **Kerem B**, Zielenski J, Markiewicz D, Bozon D, Gazit E, Rommens JM, Kennedy D, Riordan JR, Collins F and Tsui L-C. (1990) Identification of mutations in regions corresponding to the Δ ATP binding fold of the cystic fibrosis gene. *Proc Natl Acad Sci USA* 87:8447-8451.
18. Kerem E, Corey M, **Kerem B**, Rommens JM, Markiewicz D, Levison H, Tsui L-C and Durie P. (1990) Association between the Δ F508 mutation and phenotypes in cystic fibrosis. *N Engl J Med* 323:1517-1522.
19. Multiple contributors. (1990) Worldwide survey of the Δ F508 mutation - Report from the Cystic Fibrosis Analysis Consortium. *Am J Hum Genet* 47:354-359.
20. Rozen R, Schwartz RH, Hilman BC, Stanislovitis P, Horn GT, Klinger K, Daigneault J, De Braekeleer M, **Kerem B**, Tsui L-C, Fujiwara TM and Morgan K (1990). Cystic fibrosis

- mutations in North American populations of French Ancestry: Analysis of Quebec French-Canadian and Louisiana Arcadian Families. *Am J Hum Genet* 47:606-610.
21. Zielenski J, Rozmahel R, Bozon D, **Kerem B**, Grzelczak Z, Riordan JR, Rommens JM and Tsui L-C. (1991) Genomic DNA sequence of the cystic fibrosis transmembrane conductance regulator (CFTR) gene. *Genomics* 10:214-228.
22. Zielenski J, Bozon D, **Kerem B**, Markiewicz D, Durie P, Rommens JM and Tsui L-C. (1991) Identification of mutations in exons 1 through 8 of the cystic fibrosis transmembrane conductance regulator (CFTR) gene. *Genomics* 10:229-235.
23. Tsui L-C, Rommens J, **Kerem B**, Rozmahel R, Zielenski J, Kennedy D, Markiewicz D, Plavsic N, Chou JL, Bozon D and Dobbs M. (1991) Molecular genetics of cystic fibrosis. *Adv Exp Med Biol* 290:9-18.
24. Ng ISL, Pace R, Richard MV, Kobayashi K, **Kerem B**, Tsui L-C and Beaudet AL. (1991) Methods for analysis of multiple cystic fibrosis mutations. *Hum Genet* 87(5):613-617.
25. Kimchi-Sarfati C, Goitein R, **Kerem B**, Werner M, Meidan B and Schaap T (1991) Endoreduplication and polyploidy in fragile X cells induced by methotrexate and fluorodeoxyuridine: implications for diagnosis. *Am J Med Genet* 38(2-3) 429-433.
26. Dork T, Neumann T, Wulbrand U, Wulf B, Kalin N, Maab G, Krawczak M, Guillermit H, Ferec C, Horn G, Klinger K, **Kerem B**, Zielenski J, Tsui L-C and Tummeler B. (1992) Intra and extragenic marker haplotypes of CFTR mutations in cystic fibrosis families. *Hum Genet* 88:417-425.
27. Shoshani T, Augarten A, Gazit E, Bashan N, Yahav Y, Rivlin Y, Tal A, Seret H, Yaar E, **Kerem B** (1992) Association of a nonsense mutation (W1282X), the most common mutation in the Ashkenazi Jewish cystic fibrosis patients in Israel, with presentation of severe disease. *Am J Hum Genet* 50:222-228.
28. Goshen R, Kerem E, Shoshani T, Feigin E, Zamir O, Yahav Y and **Kerem B**. (1992) Cystic fibrosis presenting as undescended testis and absence of vas deferens. *Pediatrics* 90:982-983.
29. Shoshani T, Berkun Y, Yahav Y, Augarten A, Bashan N, Rivlin Y, Gazit E, Sereth H, Kerem E and **Kerem B**. (1992) A new mutation in the cystic fibrosis gene, comprised of two

adjacent DNA alterations, is a common cause of cystic fibrosis among Georgian Jews.

Genomics 15:236-237.

30. Osborne L, Gantis G, Schwarz M, Klinger K, Dork D, McIntosh I, Schwartz M, Nunes J, Anvret M, Wallace A, Williams C, Mathew C, Rozen R, Graham C, Gaparini P, Bai J, Cassiman JJ, Balassopoulou A, Davidow L, Raskin S, Kalaydjieva L, **Kerem B**, Richards S, Simon-Bouy B, Super M, Wulbrand U, Keston M, Estivill X, Vavrova V, Friedman KJ, Barton-D, Dallapiccola B, Stuhmann M, Beards F, Hill AJM, Pignatti PF, Cuppens H, Angelicheva D, Tümmler B, Brock DJH, Casals T, Macek M, Schmidtke J, Magee AC, Bonizzato A, DeBoeck C, Kuffardjieva A, Hodson M and Knight RA. (1992) Incidence and expression of the N1303K mutation of the cystic fibrosis (CFTR) gene. *Hum Genet* 89:653-658.
31. Sereth H, Shoshani T, Bashan N and **Kerem B**. (1993) Cystic Fibrosis extended haplotype and implication to the selective advantage hypothesis. *Hum. Genet* 92:289-295.
32. Benhorin J, Kalman YM, Medina A, Tzivoni D, Rave-Harel N, Dyer TD, Blangero J, MacCluer JW and **Kerem B**. (1993) Evidence for genetic heterogeneity in the long QT syndrome. *Science* 260:1960-1962.
33. Zamostiano R, Noiman S, Yahav J, Szeinberg A, **Kerem B** and Gazit E. (1993) Screening for carriers of cystic fibrosis mutations in Ashkenazi volunteers. *Harefuah* 124:202-205.
34. Augarten A, **Kerem B**, Yahav Y, Noiman S, Rivlin Y, Tal A, Blau H, Ben-Tur L, Szeinberg A, Katznelson D, Kerem E and Gazit E. (1993) Mild presentation of cystic fibrosis ... testing cystic test in patients carrying the 3849+10Kb C->T mutation. *Lancet* 342:25-26.
35. Shoshani T, Kerem E, Szeinberg A, Augarten A, Yahav Y, Cohen D, Rivlin J, Tal A and **Kerem B**. (1994) Similar levels of mRNA from the W1282X and the $\Delta F508$ cystic fibrosis alleles, in nasal epithelial cells. *J Clin Invest* 93:1502-1507.
36. Shoshani T, Augarten A, Yahav J, Gazit E and **Kerem B**. (1994) Two novel mutations in the CFTR gene: W1089X in exon 17B and 4010delTATT in exon 21. *Hum Mol Genet* 3:657-658.

37. Ginsberg G, Blau H, Kerem E, Springer C, **Kerem B**, Ackstein E, Greenberg A, Kolumbos A, Abeliovich D, Gazit E and Yahav J. (1994) Cost-benefit analysis of a national screening program for cystic fibrosis in an Israeli population. *Health Economics* 3:5-23.
38. Kalman YM, Kerem E, Darvasi A, Demarchi J and **Kerem B**. (1994) Difference in frequencies of the cystic fibrosis alleles, $\Delta F508$ and W1282X, between carriers and patients. *Eur J Hum Genet* 2:77-82.
39. Augarten A, Yahav Y, **Kerem B**, Halle D, Laufer J, Szeinberg A, Dor J, Mashiach S, Gazit E, Madgar I. (1994) Congenital bilateral absence of the vas deferens in the absence of cystic fibrosis. *Lancet* 344:1473-1474.
40. Ehrlich G, Ginzberg D, Loewenstein Y, Glick D, **Kerem B**, Ben-Ari S, Zakut H and Soreq H. (1994) Population diversity and distinct haplotype frequencies associated with ACHE and BCHE genes of Israeli Jews from Transcaucasian Georgia and from Europe. *Genomics* 22: 288-295.
41. Avner R, Laufer N, Safran A, **Kerem B**, Friedmann A and Mitrani-Rosenbaum S. (1994) Preimplantation diagnosis of cystic fibrosis by simultaneous detection of the W1282X and $\Delta F508$ mutations. *Hum Reproduct* 9:1676-1680.
42. Kerem E, Kalman YM, Yahav Y, Shoshani T, Abelyovich D, A, Rivlin J, Blau H, Tal A, Ben-Tur L, Springer C, Augarten A, Godfrey S, Lerer Israela, BD, Friedman M, **Kerem B**. (1995) Incidence of cystic fibrosis and distribution of mutations in the CFTR gene among the Jewish population of Israel. *Hum Genet* 96:193-197.
43. Darvasi A, **Kerem B**. (1995) Deletion and insertion mutations in short tandem repeats. *Eur J Hum Genet* 3:14-20.
44. Rave-Harel N, Madgar I, Goshen R, Nissim-Rafinia M, Rahat A, Chiba O, Kalman YM, Brautbar C, Augarten A, Kerem E, **Kerem B**. (1995) CFTR haplotype analysis reveals genetic heterogeneity in the etiology of congenital bilateral aplasia of the vas deferens. *Am J Hum Genet* 56:1359-1366.
45. Augarten A, Hachman S, Kerem E, **Kerem B**, Szeingerg A, Laufer J, Doolman R, Altshuler R, Blau H, Bentur L, Gazit E, Katzenelson D, Yahav Y. (1995) The significance of sweat Cl/Na ration in patients with borderline sweat test. *Pediatric Pulmonol* 20:369-371.

46. Avidor B, Zakut H, **Kerem B.** (1996) Nonradioactive simple and rapid method to detect major cystic fibrosis mutations in Ashkenazi Jews. *Clin Chem* 42:103-105.
47. Rave-Harel N, Kerem E, Nissim-Rafinia M, Madjar I, Goshen R, Augarten A, Hurwitz A, Darvasi A, **Kerem B.** (1997) The molecular basis of partial penetrance of splicing mutations in cystic fibrosis. *Am J Hum Genet* 60:87-94.
48. Kerem E, Rave-Harel N, Augarten A, Madgar I, Nissim-Rafinia M, Yahav Y, Goshen R, Bentur L, Rivlin J, Aviram M, Genem A, Chiba O, Kremer MD, Simon A, Branski D, **Kerem B** (1997) A CFTR splice mutation with partial penetrance associated with variable cystic fibrosis presentation. *Am J Respir Crit Care Med* 155:1914-1920.
49. Estivill X, Bancells C, Ramos C, and the Biomed Mutation Analysis Consortium (1997) Geographic distribution and regional origin of 272 cystic fibrosis mutations in European populations. *Hum Mutation* 10:135-154.
50. Kerem E, Nissim-Rafinia M, Argaman Z, Augarten A, Bentur L, Klar A, Yahav Y, Szeinberg A, Chiba-Falek O, Branski D, Corey M, **Kerem B** (1997) A missense cystic fibrosis transmembrane conductance regulator mutation with variable phenotype. *Pediatrics* 100: 1-6.
51. Falek-Chiba O, Nissim Rafinia M, Argaman Z, Genem A, Moran I, Kerem E, **Kerem B** (1997) Screening of CFTR mutations in an isolated population: identification of carriers and patients. *Eur J Hum Genet* 6: 181-184.
52. Augarten A, Katznelson D, Dubenbaum R, Sela BA, Luski A, Szeinberg A, **Kerem B**, Paret G, Sack J, Yahav Y (1998) Serum lipase levels pre and post Lundh meal: evaluation of pancreatic status in cystic fibrosis. *Int J Clin Lab Res* 28:226-229.
53. Benhorin J, Goldmit M, MacCluer JW, Blangero J, Goffen R, Leibovitch A, Rahat A, Wang Q, Medina A, Towbin JA, **Kerem B** (1998) Identification of a new SCN5A mutation associated with the long QT syndrome. *Hum Mutation* 12(1):72.
54. Mishmar D, Rahat A, Scherer SW, Nyakatura G, Hinzmann B, Kohwi Y, Mandel-Gutfroind Y, Lee JR, Drescher B, Sas DE, Margalit H, Platzer M, Weiss A, Tsui L-C, Rosenthal A, **Kerem B.** (1998) Molecular characterization of a common fragile site (FRA7H) on human chromosome 7 by the cloning of an SV40 integration site. *Proc Natl Acad Sci USA* 95:8141-8146.

55. Guttenbach M, Nasssar N, Feichtinger W, Steinlein C, Nanda I, Wanner G, **Kerem B**, Schmid M (1998) An interstitial nucleolus organizer region in the long arm of chromosome 7: cytogenetic characterization and familial segregation. *Cytogenet Cell Genet* 80:104-112.
56. An RH, Wang XL, **Kerem B**, Benhorin J, Goldmit M, Kass RS (1998) A novel LQT-3 mutation affects Na channel activity through interactions between α and β_1 subunits. *Circulation Research* 83:141-146. (IF 9.19; IR 2/63 in Cardiac and cardiovascular system;
57. Chiba-Falek O, Kerem E, Shoshani T, Aviram M, Augarten A, Bentur L, Tal A, Tullis E, Rahat A, **Kerem B** (1998) The molecular basis of disease variability among cystic fibrosis patients carrying the 3849+1-kb C-T mutation. *Genomics* 53:276-283.
58. Gross-Tsur V, Manor O, **Kerem B**, Friedlander Y, Shalev RS (1998) Developmental dyscalculia is a familial learning disability. *Ann Neurology* 44: 542-546.
59. Mishmar D, Mandel-Gutfreund Y, Margalit H, Rahat A, **Kerem B** (1999) Common fragile Sites: G band characteristics with an R-band? *Am J Hum Genet* 64:908-910.
60. Wilschanski M, Rivlin J, Cohen S, Augarten A, Blau H, Aviram M, Bentur L, Springer C, Vila Y, Branski D, **Kerem B**, Kerem E (1999) Clinical and genetic risk factors for cystic fibrosis-related liver diseases. *Pediatrics* 103:52-57.
61. Chiba-Falek O, Parad RB, Kerem E, **Kerem B** (1999) Variable levels of normal RNA in different organs carrying the CFTR splicing mutation 3849+10kb C->T. *Am J Respir and Critical Care Medicine* 159:1998-2002.
62. Wilschanski M, Famini C, Blau H, Rivlin J, Augarten A, Avital A, **Kerem B** and Kerem E (2000) A Pilot study of the effect of Gentamicin on nasal potential in cystic fibrosis patients carrying stop mutations. *Am. J. Respir. Crit. Care Med.* 161: 860-865.
63. Benhorin J, Taub R, Goldmit M, **Kerem B**, Kass RS, Windman I, Medina A. (2000) Effects of Flecainide in patients with a new SCN5A mutation: mutation-specific therapy for long QT syndrome? *Circulation* 101:1698-1707.
64. Hellman A, Rahat A, Scherer SW, Darvasi A, Tsui L.-C, **Kerem B** (2000) Replication delay along FRA7H, a common fragile site on human chromosome 7, leads to chromosomal instability. *Mol Cell Biol* 20: 4420-4427.

65. Nissim-Rafinia M, Chiba-Falek O, Sharon G, Boss A, **Kerem B** (2000) Cellular and viral splicing factors can modify the splicing pattern of CFTR transcripts carrying splicing mutations. *Hum Mol Genet* 9:1771-1778.
66. Abriel H, Wehrens XH, Benhorin J, **Kerem B**, Kass RS (2000) Molecular pharmacology of the sodium channel mutation D1790G linked to the long-QT syndrome *Circulation* 102:921-925.
67. Wilschanski M, Famini H, Strauss Liviatan N, Rivlin J, Blau H, Bibi H, Bentur L, Yahav Y, Springer H, Kramer MR, Klar K, Ilani A, **Kerem B**, Kerem E. (2001) Nasal potential difference measurements in patients with atypical cystic fibrosis. *Eur Respir J* 17:1208-1215.
68. Shalev RS, Manor O, **Kerem B**, Ayali M, Badichi N, Friedlander Y, Gross-Tsur V (2001) Developmental dyscalculia is a familial learning disability. *Journal of Learning Disabilities* 34 (1): 59-65.
69. Hellman A, Zlotorynski E, Scherer SW, Cheung J, Vincent JB, Smith DI, Trakhtenbrot L, **Kerem B** (2002) A role for common fragile site induction in amplification of human oncogenes. *Cancer Cell* 1: 89-97.
70. Benhorin J, Moss AJ, Bak M, Zareba W, Kaufman E, **Kerem B**, Towbin JA, Priori S, Kass RS, Attali B, Brown A and Ficker E. (2002) Variable Expression of Long QT syndrome among gene carriers from families with five different HERG mutations. *Ann Noninvasive Electrocardiol* 7 40-46.
71. Zoosmann-Diskin AJ, Liron JA, **Kerem B**, Shohat M, Peleg L (2002) Protein electrophoretic markers in human complement C3 and C4 genetic affinities. *Ann Hum Bio* 29:142-175.
72. Lerer B, Segman RH, Hamdan A, Kanyas K, Karni O, Kohn Y, Korner M, Lanktree M, Kaadan M, Turetsky N, Yakir A, **Kerem B**, Macciardi F (2003) Genome scan of Arab Israeli families maps a schizophrenia susceptibility gene to chromosome 6q23 and supports a locus at chromosome 10q24. *Molecular Psychiatry* (in press).

Invited Reviews

73. Kerem E, and **Kerem B.** (1995) The relationship between genotype and phenotype in cystic fibrosis. *Curr Opin in Pulm Med* 1: 450-456.
74. **Kerem B,** and Kerem E. (1996) The molecular basis for genotype-phenotype correlation in cystic fibrosis. *Eur J Hum Genet* 4:65-73.
75. **Kerem B,** and Kerem E. (1996) The molecular basis for disease variability in cystic fibrosis. *Cellular Pharmacology* 34:163-169.
76. Kerem E, and **Kerem B.** (1996) Genotype-Phenotype correlation in cystic fibrosis. *Pediatric Pulmonol* 22:387-395.
77. **Kerem B,** Chiba-Falek O, Kerem E. (1997) Cystic fibrosis in Jews: frequency and distribution of mutations. *Genetic testing* 1:35-39.
78. Nissim-Rafinia M and **Kerem B,** (2001) Alternative splicing regulation as a genetic modifier. *Trends in Genetics* 18:123-127.

Chapters in books

79. **Kerem B.** (1993) "Cystic fibrosis" in the new edition of *The Hebrew Encyclopedia*.
80. Ehrlich G, Ginzberg D, Schwarz M, Loewenstein Y, Glick D, **Kerem B,** Ben-Ari S, Zakut H, Soreq H. (1995) Population diversity of point mutations in the human ACHE and BCHE genes predicts variable responses to anti-cholinesterase drugs. In: Alzheimer's and Parkinson's Diseases: Recent advances. Hanin I, Fisher A and Yoshida M Eds. Plenum

Fig. 2

**Restoration of the CFTR function
by splicing factors (081301k)**

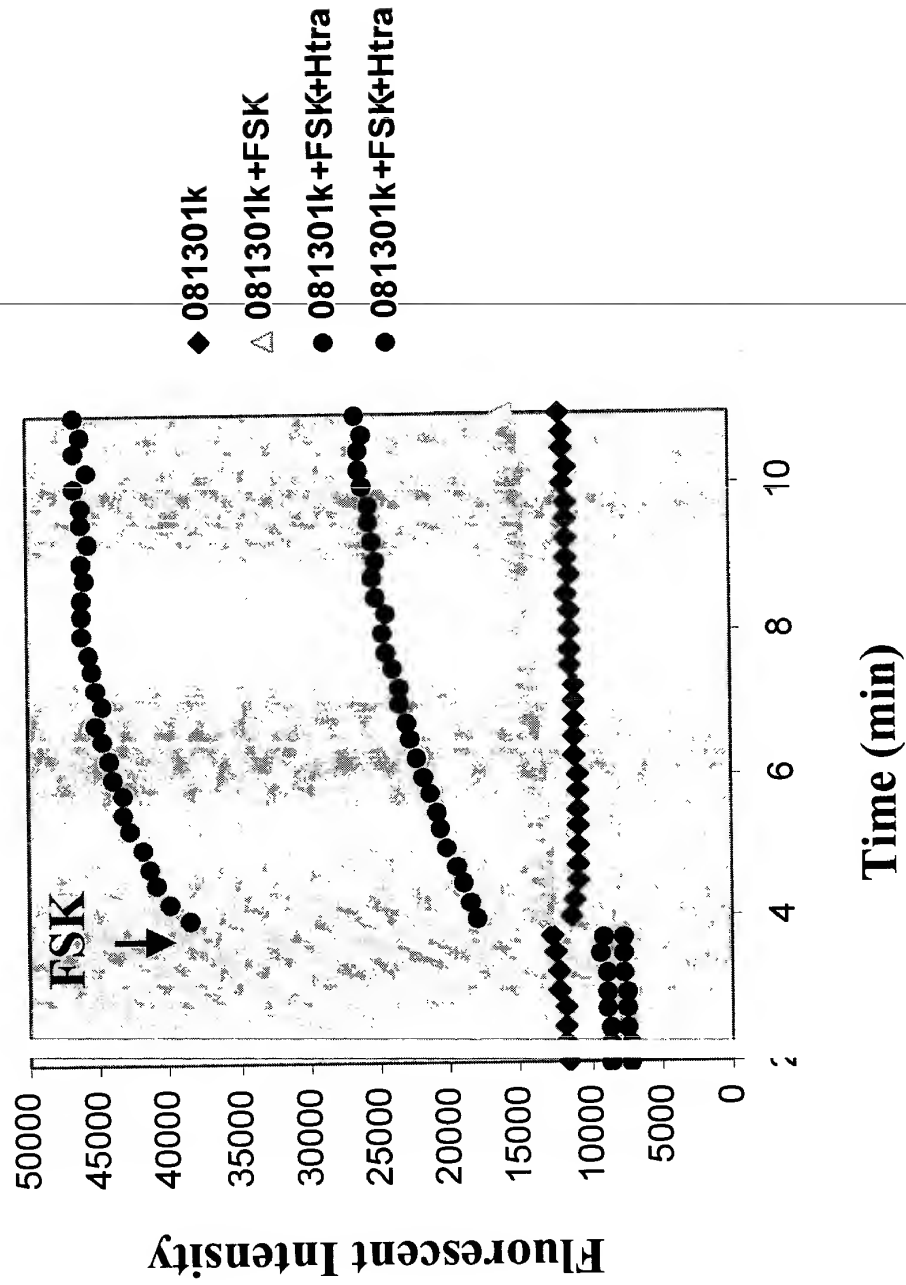
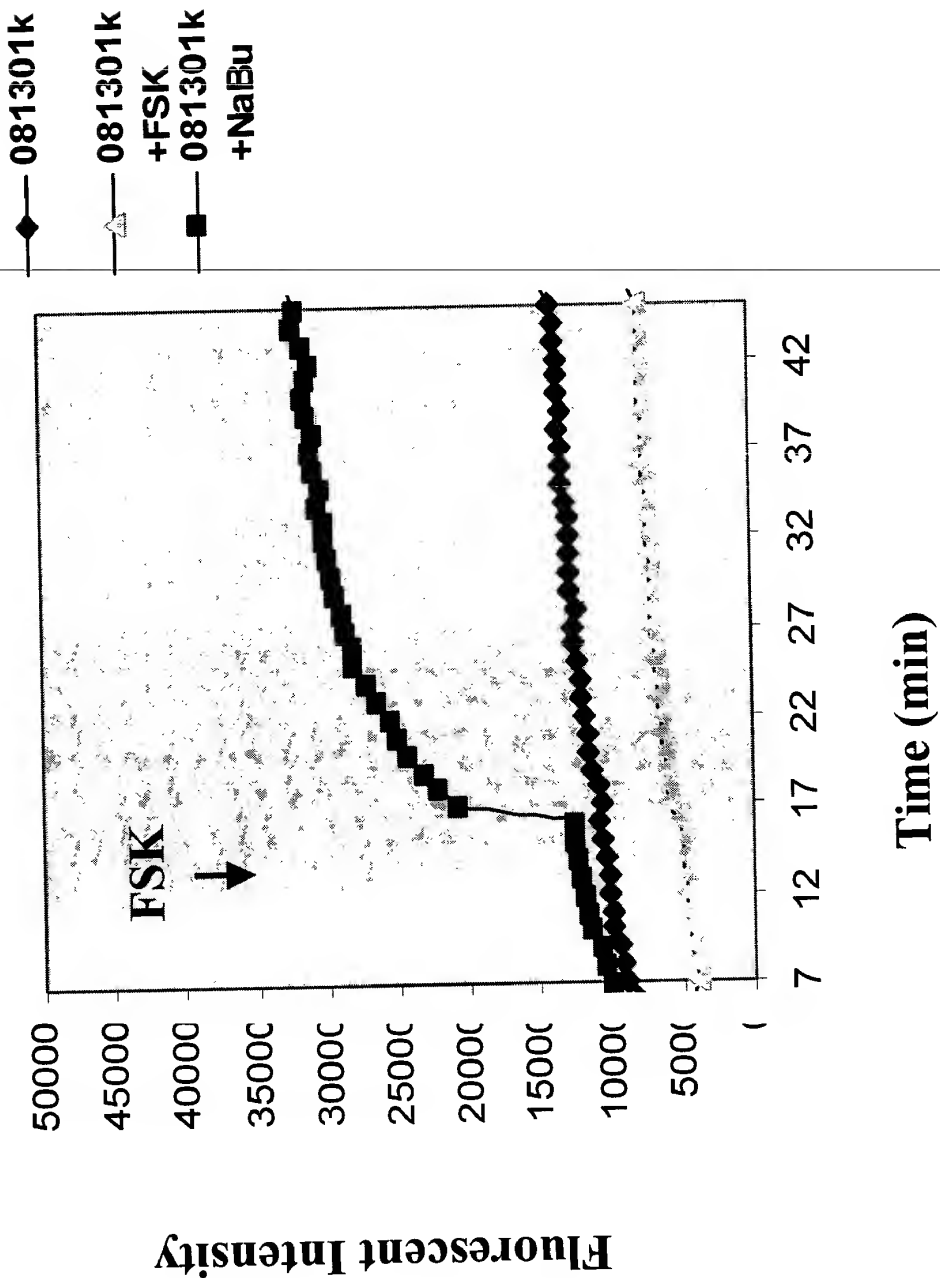


Fig. 3

**Restoration of the CFTR function
by sodium butyrate (081301k)**



Annex B,
Kerem Declaration
09/871,809

Fig. 4

**Restoration of the CFTR function
by sodium butyrate (091398k)**

